191. (withdrawn) The pharmaceutical composition of Claim 178, wherein the drug is a boron compound.

192. (withdrawn) The pharmaceutical composition of Claim 178, wherein the drug is an anti-convulsant.

193. (withdrawn) The pharmaceutical composition of Claim 178, wherein the drug is an anti-trauma agent.

194. (withdrawn) The pharmaceutical composition of Claim 178, wherein the drug is a diagnostic agent

195. (withdrawn) The kit of Claim 108, wherein the agonist is minoxidil sulfate.

196. (withdrawn) The kit of Claim 108, wherein the agonist is pinacidil.

197. (withdrawn) The kit of Claim 108, wherein the agonist is cromakalim.

198. (withdrawn) The kit of Claim 108, wherein the agonist is levcromakalim.

199. (withdrawn) The kit of Claim 108, wherein the agonist is diazoxide.

REMARKS

Claims 1-6, 11-18, 97-100 and 106-199 are pending in the present application. Claims 97-100, 106-109, 124-138, 140-152, 156-199 are withdrawn from consideration pursuant to 37 CFR 1.142(b) as directed to a non-elected invention or non-elected species in the absence of an allowable generic claim. Claims 11 and 12 have been amended for clarity.

Claims 1-6, 11-18, 110-152 are directed to a method of delivering a medicant to an abnormal brain region comprising administering an ATP-sensitive potassium channel agonist and a medicant. Claims 153-155 are directed to a method of delivering a medicant to an abnormal brain region comprising administering minoxidil or minoxidil sulfate and a medicant.

Claims 97-100, 106-107 and 167-177 are directed to a pharmaceutical composition including a combination of an ATP sensitive potassium channel agonist and a therapeutic cytotoxic agent. Claims 178-194 are directed to a pharmaceutical composition comprising an ATP-sensitive potassium channel agonist and a drug.

Claims 108-109 and 195-199 are directed to a kit for enhancing the delivery of a medicant to an abnormal brain region comprising an agonist of an ATP sensitive potassium channel and instructions.

Rejection under 35 USC § 112

The claims as pending have been rejected under 35 USC § 112 as non-enabled. The Examiner states that it would be unpredictable whether the invention would be applicable to the treatment of any disease or disorder. The Examiner further states that the specification does not demonstrate delivery of an amount of any therapeutic agent sufficient to produce a therapeutic effect. The Examiner notes that delivery of macromolecules of therapeutic value requires intracerebral or intracerbroventricular injection or infusion using osmotic pumps. The Examiner further suggests that a variety of factors can affect therapeutic outcome, including method of delivery and site of delivery, as well as composition uptake, half-life and mode of action. Finally, the Examiner suggests that it would be reasonable to expect that different combinations of channel agonists and medicants will have varying degrees of effect.

In response to these rejection, the Applicants direct the Examiner's attention to (i) a paper recently published by the Applicants in a highly respected scientific publication (Ningaraj NS, Rao MK and Black KL Cancer Research (2003) 6324) 8899-911); and (ii) the Declaration of Dr. Keith Black (The Declaration is provided herewith and includes the Cancer Research paper as Exhibit A). Together, these documents present data establishing that the method of the present invention permits delivery of varied therapeutic agents to a range of abnormal brain regions through varied modes of administration.

(i) Disease or Disorder

The Examiner suggests that the present invention is not enabled for the treatment of brain-based diseases or disorders generally. Until the Applicants' discovery thereof, it was not known that brain microcapillary endothelial cells adjacent to tumor cells overexpress K_{ATP} channels and therefore represent targets for BTB permeability modulation. The specification shows that when rats bearing implanted glioma cells are infused with minoxidil sulfate (MS) (a K_{ATP} channel activator), permeability to ([^{14}C] AIB) is selectively increased (see page 18, lines 13-20, and Figure 1A and 1B). The Applicants direct the Examiner's attention to the Cancer Research paper referenced above, which establishes that K_{ATP} channels mediate the MS-induced increase in BTB permeability in glioma-bearing rat brains. (Figure 2).

The Applicants further direct the Examiner's attention to Dr. Black's Declaration, which shows that enhanced drug delivery to abnormal brain regions is not limited to primary brain tumors. Rather, the Declaration presents experimental results establishing enhanced uptake of compound in metastatic breast brain tumors and metastatic lung brain tumors (Exhibits C and D). Experimental evidence is also provided to establish that K_{ATP} channels are overexpressed in metastatic brain tumors of diverse origin, including lung, breast and renal cancers, as well as in the microcapillary endothelial cells adjacent to those tumors (Exhibit B). The Cancer Research paper also establishes that abnormal cells actually directly enhance the expression of K_{ATP} channels on endothelial cells (Figure 6).

With respect to non-cancerous abnormal brain regions, K_{ATP} channels have been shown to be overexpressed in hypoxic and ischemic conditions (Kitazano T et al. Stroke (1995) 26: 1713-1723. In view of this evidence, Applicants believe that the claims are enabled for abnormal brain regions generally, and in particular, for malignant brain tumors.

(ii) Medicants

The Examiner suggests that the present invention is not enabled for delivery of any therapeutic agent, and in particular, for macromolecules of therapeutic value. The Applicants direct the Examiner's attention to the Cancer Research paper referenced above, which establishes the selective delivery of a range of molecules across the blood brain barrier, including therapeutic macromolecules. Figure 3 on page 8904 shows that co-administration of MS enhances delivery of [^{14}C] AIB, dextran and carboplatin (CPN), which has a molecular weight of

371KD. Figure 5 on page 8906 shows that co-administration of MS enhances the delivery of adenovirus coding for green fluorescent protein (adv-GFP) as well as Her-2 monoclonal antibody (MAb) and Neu polyclonal antibody. Moreover, enhanced delivery is shown to be *selective* to abnormal brain regions versus normal brain regions. Figure 3 on page 8904 shows that co-injection of MS increases the uptake of compounds is specific to the tumor center (vs. the brain surrounding the tumor or the contralateral brain). Applicants believe that the claims are enabled for medicants generally, and in particularly, for therapeutic macromolecules.

(iii) *Delivery*

The Examiner notes that the delivery of macromolecules of therapeutic value to the brain requires intracerebral or intracerbroventricular injection or infusion by osmotic pumps (citing Sabate et al. Clin Neurosci. (1996) 3(5):317-21). The Applicants agree with the Examiner's characterization of the prior art, but note that the present invention is designed to overcome that very limitation. The specification shows that *intracarotid infusion* of minoxidil sulfate into the right carotid artery enhances the delivery of [^{14}C]AIB across the blood tumor barrier (page 18, lines 12-20). Dr. Black's Declaration provides experimental evidence to establish that the present invention is not limited to intracarotid delivery. Rather, *intravenous delivery* of minoxidil sulfate is shown to effectively increase the delivery of compounds to abnormal brain regions (See Exhibits C and D). In view of this evidence, Applicants believe that the claims are enabled for systemic delivery generally, and in particularly, for intracarotid and intravenous delivery.

Conclusion

In light of the comments provided herein, Applicants request that the Examiner now allow all pending claims.

Respectfully submitted,
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